

Dr. Edward D. Freis

Proving the value of antihypertensive therapy

—By Hugh Bloom and June Nusser

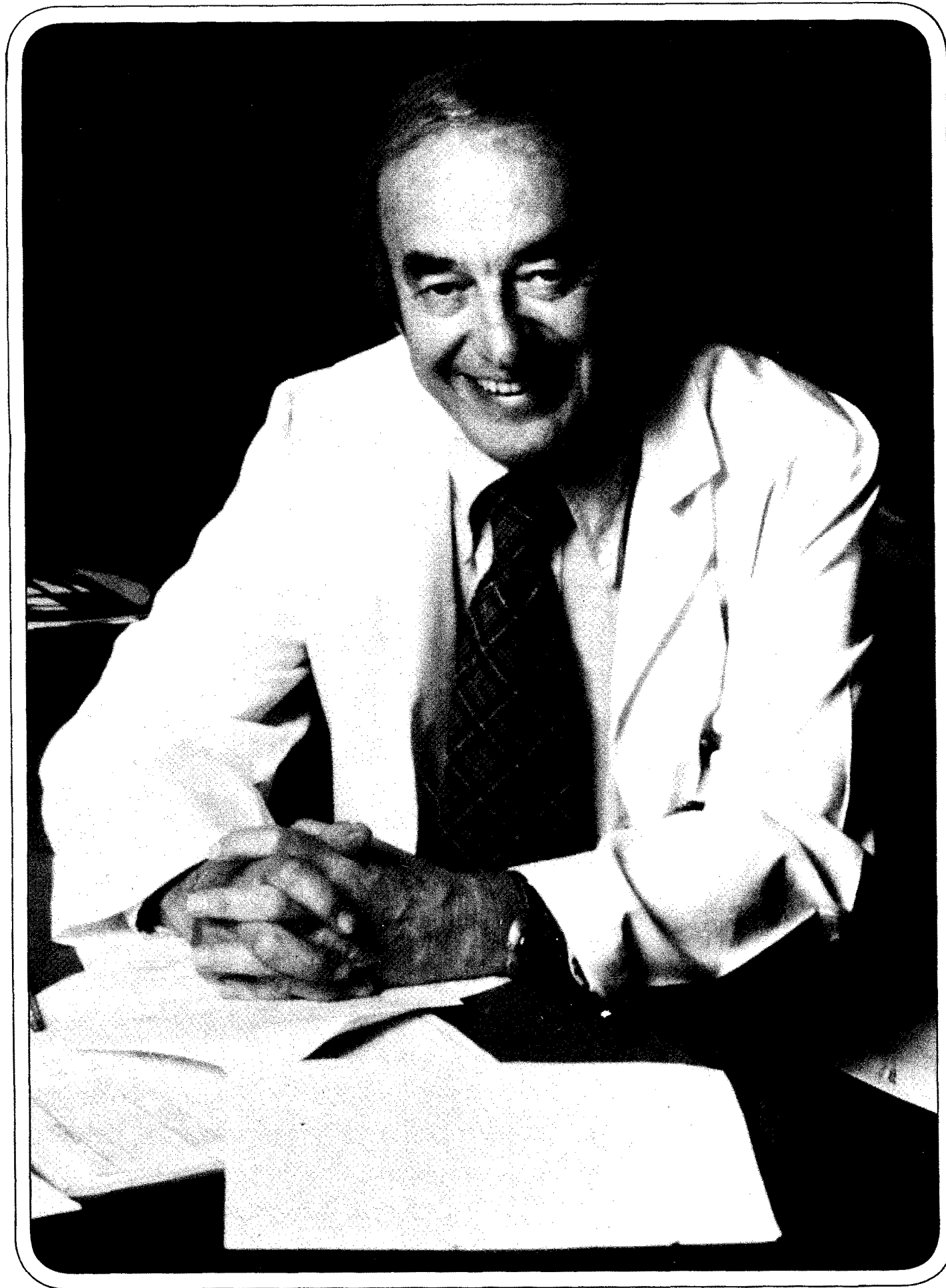
PICTURE AN INTERNIST'S OFFICE in the early 1960s. The patient is a 36-year-old black man in for an annual check-up. After completing the examination, the physician says, "You're in fine shape." He does have a slight reservation, which he shares with the patient: "Your blood pressure is higher than normal—150/100—but, that's nothing to worry about."

Indeed, if this hypothetical physician, considering a course of antihypertensive drug therapy, had consulted the then latest edition of Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, he would have read that antihypertensive drug therapy was "purely symptomatic and the underlying pathological process is not altered." Insurance company studies had documented an unfavorable effect on life expectancy of blood pressure, but it was not clear that there was any way to alter that association. Untreated, that hypothetical patient would probably now be either dead, felled by stroke or heart or kidney failure, or suffering from one of the chronic complications of hypertension.

A decade later, this patient's fate and his doctor's reaction to his blood pressure would be quite different, because by 1970 it was proven that persistent hypertension in the high-risk group (under 45 years of age, male, and, especially, black) responds to immediate drug therapy which can prevent hypertensive complications. The modern physician's edition of Goodman and Gilman states unequivocally that "in almost all cases of hypertensive cardiovascular disease, the blood pressure can be successfully controlled by skillful use of the drugs currently available."

The cause of this dramatic reversal in medical thinking, the work that amplified "the silent disease" into a clear call of danger, was the publication of the Veterans Administration Cooperative Study Group on Antihypertensive Agents directed by the Senior Medical Investigator at the Washington, D.C. Veterans Administration Medical Center, Dr. Edward David Freis.

Although his decades of research into cardiovascular disease had made Dr. Freis suspect that hypertension was



Dr. Edward Freis—the physician who directed the VA Cooperative Study which conclusively proved the value of antihypertensive agents in preventing stroke, congestive heart failure, and malignant hypertension—comments on the study, on the status of care of the hypertensive, and on the future of preventive medicine.

both dangerous and treatable, no large adequately controlled clinical trial had been performed. A group of physicians in the early 1960s questioned whether essential hypertension was a significant factor in disease and whether treatment had any appreciable benefit. These skeptics were not easily silenced. Dr. Freis recalls attending meetings where he was told, "Physicians who use antihypertensive drugs are treating the blood pressure cuff and not the patient." There were heated arguments with physicians who believed it was unnecessary to treat this asymptomatic condition ("benign" hypertension) with drugs that may produce some serious side effects and that had to be continued over the entire lifetime of the patient. The extent of the controversy about whether high

blood pressure should be treated gave ethical sanction to the study—in which men who received placebos died and experienced significant complications from their hypertension.

Accordingly, in 1963 Dr. Freis began the now-famous cooperative studies of 523 male hypertensive patients in 17 VA Hospitals. Patients were randomly assigned to the double-blind drug therapy trials (reserpine plus hydralazine plus hydrochlorothiazide, or placebo) and divided into two subgroups, one containing 380 patients with mild-to-moderate hypertension (diastolic blood pressure averaging between 90 and 114 mm Hg) and another group of 143 patients whose hypertension was considered moderately severe (diastolic pressure of 115 mm Hg to 129 mm

Hg). The study used a selected population with uncooperative and unreliable patients eliminated from the trial. Prophetically, Dr. Freis said at the time, "Treatment obviously would have not been as effective in a group of patients less carefully selected with regard to their desire to cooperate."

All patients receiving the active drugs were given the same dose. "This isn't standard practice but we were dealing with 17 different hospitals and 17 groups of doctors. We wanted to make sure none of the patients would be undertreated. I was afraid that if we started with a single drug we wouldn't get the optimum reduction in blood pressure. We did succeed in getting pressure down to normal, or near normal, in a majority of those who received active medication," Dr. Freis

recalls. The report on the results of therapy in the moderately severe hypertensives appeared in 1967 (*JAMA* 202:1028, 1967), and the report on the mild-to-moderate hypertensives appeared three years later (*JAMA* 213:1143, 1970).

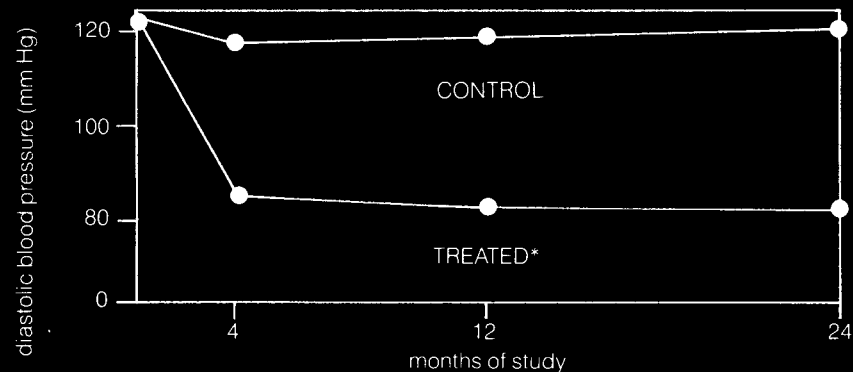
Untreated had major complications

Of the patients with moderately severe hypertension, 27 of the untreated group developed major cardiovascular complications, including congestive heart failure, dissecting aneurysm, stroke, and malignant hypertension. Four of these patients died. In contrast, only one patient in the treated group developed a hypertensive complication, a mild stroke. Only one potentially drug-related complication was reported: a case of mental depression.

Ability to control hypertension

VA COOPERATIVE STUDY, 1967

Men with diastolic pressure between 115 and 129 mm Hg

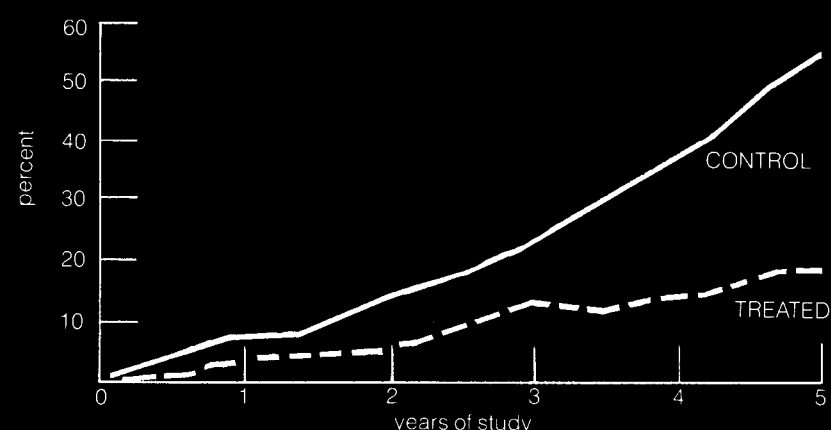


*50 mg hydralazine (or hydralapril) and 0.1 mg reserpine and 75 to 150 mg hydrochlorothiazide

Morbid events in treated and control patients

VA COOPERATIVE STUDY, 1970

Men with diastolic pressure between 90 and 115 mm Hg



Effect of treatment on mortality and major nonfatal events

VA COOPERATIVE STUDY 1967 AND 1970

Pretreatment mean diastolic BP	Mean followup period	Percent experiencing events control	Percent experiencing events treated	Percent improved by treatment*
90-114 mm Hg	40 months	39.3%	11.8%	70%
115-129 mm Hg	18 months	38.6%	2.7%	93%

*Percent improved calculated by the difference between percent experiencing events in control and treated groups divided by percent experiencing events in placebo group

DR. EDWARD FREIS *continued*

Treatment did not affect the rate of atherosclerotic complications or myocardial infarction.

"These patients were studied only for an average of 18 months," Dr. Freis reported, "because of the high incidence of major hypertensive complications occurring in the placebo group."

Patients with mild hypertension were followed for at least three and a quarter years with some of the group studied for five years or more. There were 19 cardiovascular deaths in the control group—more than twice the eight suffered by the treated patients.

The results of the VA Cooperative

studies startled the medical community: drug therapy for moderately severe hypertension reduced the death rate by more than 50%. Moreover, antihypertensive agents were proved to be 67% effective in preventing major complications.

This work won Dr. Freis the Albert Lasker Clinical Research Award in 1971 because it "offers a momentous opportunity to clinical medicine. It is an exemplary demonstration of the potential of preventive medicine for saving and prolonging the lives of tens of thousands of Americans."

It would be comforting to believe

that Dr. Freis' clear demonstration of the value of antihypertensive therapy

The skeptics: "Physicians who use antihypertensive drugs are treating the blood pressure cuff and not the patient."

was immediately translated into clinical practice, but unfortunately this was

not the case. A full five years after the publication of the studies, Dr. Freis wrote that "it would be expected that the results of these well controlled therapeutic trials demonstrating the value of effective antihypertensive drug treatment in the prevention of stroke would be widely recognized and immediately applied by the medical profession. The available evidence, however, indicates the opposite. In addition to the widespread lack of awareness of the medical profession of the benefits of treatment, there is also a failure of detection of hypertension in large segments of the population."



then I went at it again about 15 years ago." Even after the long hiatus, his talent survived intact. He won the Laurel Pines club championship in 1967 and was the district medalist for the U.S. Golf Association National Seniors competition in 1971.

During his premed years at the University of Arizona, he met Willa Hussey and the young couple were married

In 1962, the Cardiovascular Study Section of the NIH met at Stone House in Bethesda. Among those present, Dr. Freis is sitting on the steps, to the left is Nobel Laureate Dr. Andre Cournand, in front of the window is Dr. Homer Smith, and sitting below Dr. Smith is Dr. Donald Fredrickson (holding a cigarette).

in 1934. Two years later, the Freis couple moved to New York, where he attended Columbia University College of Physicians and Surgeons, receiving his M.D. in 1940. After an internship at Boston's Massachusetts Memorial Hospital and a residency at Boston City Hospital, Dr. Freis joined the Army Air Force.

The army years confirmed his commitment to research. "I was assistant chief of a pathology lab in a big Air Force hospital in Lincoln, Nebraska," he recalled. "There I worked with Ferdinand Helwig, a German-trained pathologist who carried on the grand tradition of the 'microbe hunters' de-

Today, Dr. Freis is a bit more optimistic. "I believe the general public is much more aware of hypertension than ten years ago," Dr. Freis affirmed, "and that they now consider it to be a serious condition. But, more education is always needed because this is an important disease with a high risk, involving, according to the latest figures, about one quarter of the American population." Still, physicians can't spend the time to properly educate patients and follow their hypertension. Dr. Freis advocates development of community hypertension clinics all over the country, run by a single physician supported by many nurses. "I think hypertensive patients will receive better care in these clinics than in the average physician's office."

Preventive medicine is a passion with the affable, athletic, 66-year-old physician, and he is justly proud of his contribution to a concept that is often praised but not always followed by the medical community. "We don't have the same evidence of benefit in the prevention of cancer, even with all the annual examinations, and we don't have evidence in heart disease yet, but with respect to the preventive aspects of hypertension treatment, no one can scoff if he knows the facts."

Born in Chicago on May 13, 1912, Edward Freis was raised on a farm 30 miles from the city. It was a healthy, happy life for the boy who "did a lot of wandering around, looking at nature, and reading books beyond my years." The books that interested him most were Paul de Kruif's fascinating studies of the giants of medical research, and "when I decided to become a physician," Dr. Freis recalled, "I tried to go in for research right from the beginning. Right from the beginning, too, it was the circulation: heart, blood vessel disease, coronary disease, hypertension."

Young Ed's parents moved to Chicago when he was 12, and it was there that he discovered another life-long passion, golf—"the only thing I enjoy more than research." His handicap is 5. "I was a competitive golfer since high school days," Dr. Freis recounted, "and I played on the college team at the University of Arizona. I stopped playing competitively for more than 20 years during the period when I was doing major work, and

scribed by de Kruif. His scientific integrity and sense of medical history were an inspiration to me." Another inspiration during the Air Force years was internist and psychiatrist Dr. I. Arthur Mirsky, with whom Freis worked in Nebraska. "He made me feel that research was a very exciting and stimulating enterprise—like prospecting for gold."

After the war, in 1946, young Dr. Freis returned to Boston to complete his residency in internal medicine—and to begin his career as a researcher. Surgical sympathectomy was the popular treatment for hypertension in those days, Dr. Freis points out, and his chief at Massachusetts Memorial

Hospital, Dr. Robert Wilkins, was involved with the assessment of the cardiovascular and circulatory changes associated with this procedure. Dr. James A. Shannon, later head of the NIH, was then the Director of the Squibb Institute for Medical Research, and he asked Dr. Wilkins and Massachusetts Memorial Chief of Medicine, Dr. Chester S. Keefer, to work with the Institute in an investigation of the chemotherapeutics of hypertension. The fledgling researcher was charged with the evaluation of any drugs that might emerge in the project.

The first drug tested was the antimalarial agent, pentaquine, a derivative of 8-aminoquinoline which had been developed during World War II in a search for more potent and less toxic compounds than primaquine. A known side effect of the drug in dosages larger than those used in malaria was orthostatic hypotension. Dr. Freis found that although pentaquine indeed lowered blood pressure (dramatically in one patient with malignant hypertension), it proved too toxic for human use. With his colleague, Dr. Joseph Stanton, he then combed the literature in search for an effective, safe antihypertensive. Impressed by the studies of Harvard's Dr. Otto Kraye into the veratrum alkaloids, the researchers began trials of veratrum viride, a powder prepared from the roots of a plant commonly called swamp helibore or Indian poke.

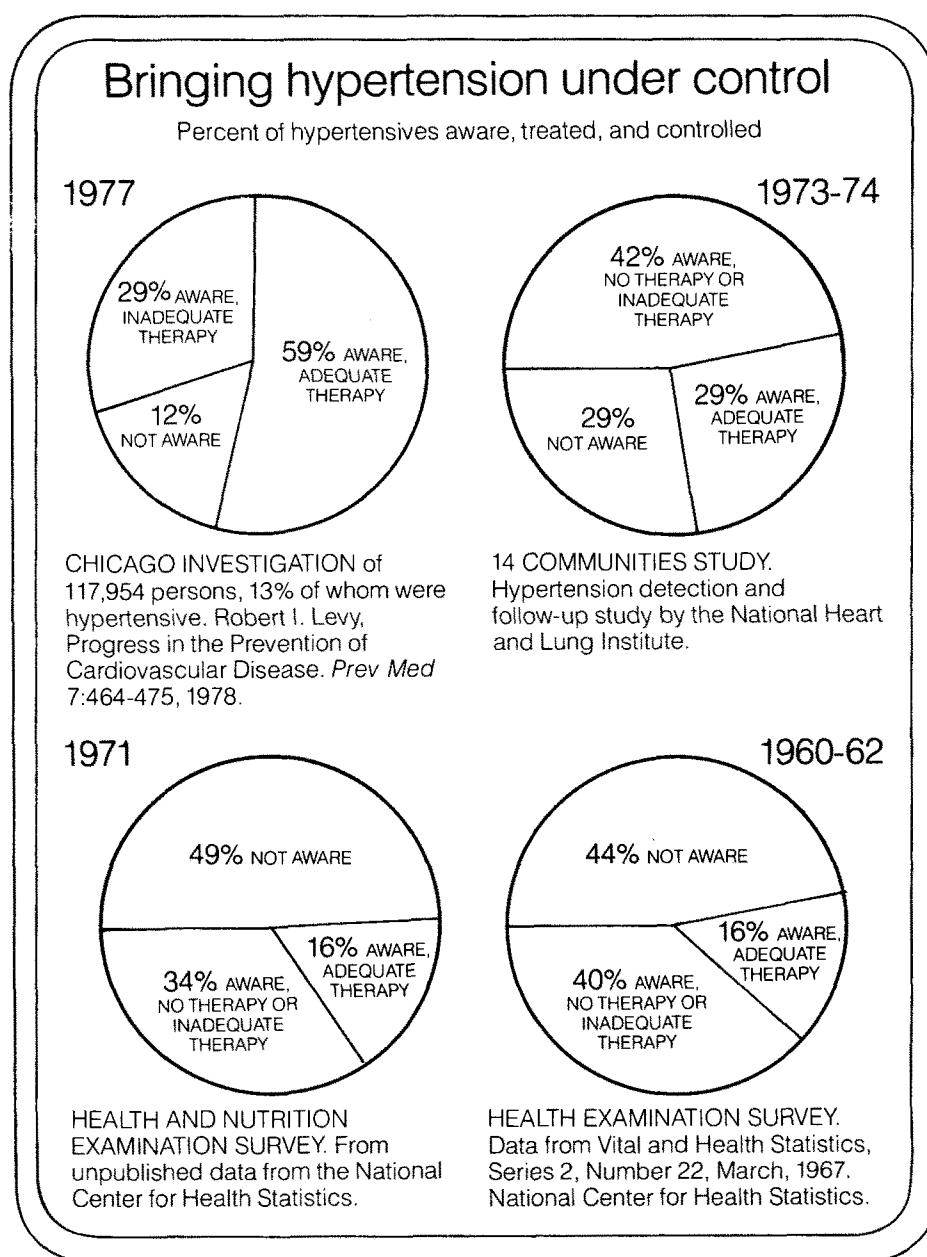
"The FDA should require food processors to put an easily identifiable label on food stating whether it is high or low in salt."

Unlike pentaquine, effective doses of veratrum proved to be nontoxic, and Dr. Freis reported that intravenous injection of this agent was particularly effective in patients with congestive heart failure.

In 1949, Dr. Freis left Boston to join the faculty of Georgetown University in Washington, D.C., an association that continues to this day—he now occupies the position of Professor of Medicine.

Dr. Freis has continued his investigation of the clinical pharmacology and therapeutics of antihypertensive agents and, over the three decades of his interest, he has been involved in the development of virtually every antihypertensive drug now used in the U.S. His studies of the mechanism of action of the thiazide diuretics—the cornerstone of modern antihypertensive therapy—were instrumental in emphasizing the importance of volume depletion in the management of high blood pressure.

In 1960, Dr. Freis, in a classic review of the hemodynamics of hypertension, proposed the phrase "cardiogenic hypertension," to acknowl-



While probably not representative of the treatment of hypertension in general, data from these health surveys show that with a concerted community effort, hypertension is increasingly being brought under control. Note the substantial increase in patients who are aware and adequately controlled.

edge the active role of the heart in hypertension. His premise was that blood pressure was a direct correlate of both cardiac output and peripheral resistance. Increased cardiac stimulation and resulting increased output could be responsible for hypertension. The identification of the hemodynamics of

Dr. Freis advocates the development of community hypertension clinics all over the country, run by a single physician supported by many nurses.

hypertension, which is now quite advanced, finds its roots in Dr. Freis' assessment of cardiac output. His theory was altered in the research that followed: it is now seen that increased cardiac output may play a role in the initiation of hypertension, but that it is not essential for the continued maintenance of hypertension.

Although Dr. Freis' studies conclusively proved that essential or primary hypertension is a treatable disease and

that the treatment protects against cardiovascular complications, the cause of the condition is still an enigma. Hypertension is popularly thought of as associated with life's "tensions"—but the link is not to emotional stress, it is believed, but to the quantity of salt in the diet.

"Stress will certainly raise blood pressure," Dr. Freis commented, "but it does not cause hypertension. Blood pressure in both hypertensive and normotensive individuals fluctuates by as much as 50 mm of mercury during a 24-hour period." This fluctuation in blood pressure is very important in the diagnosis of hypertension, Dr. Freis underlined. No patient, he believes, should be treated until he has had at least two, and ideally, three, readings.

What of the increased incidence of hypertension, estimated at 15% of the population 10 years ago and seen as affecting 27% of Americans in a current survey? Dr. Freis has no explanation for the increase, but he cautions against finding a causal role for stress in the environment in high blood pressure. "Data from studies carried out by the U.S. Bureau of Vital Statistics," he pointed out, "show that the executive is less likely to be hypertensive than the laborer. Inhabitants of the rural South have more, not less, hyperten-

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sion than dwellers in the big Northern cities."

What about primitive societies? "It is true," Dr. Freis agreed, "that there is little or no hypertension in primitive societies that are completely isolated—and there is no correlation between advancing age and advancing blood pressure as is found in our society. The correlation found in primitive life, however, is not with a lack of nervous excitement but with the absence of salt in the diet. As soon as salt is introduced into the isolated primitive group, these people begin to show as much hypertension as we do, even if their life-style is little changed."

If salt can cause hypertension, does eliminating it from the diet cause a drop in pressure? "Of course, but restricting salt intake is not a very practical approach to treatment because it's so hard to get the patient to do it. You have to reduce the salt to such a minute amount that it becomes impractical. What we need," he advised, "is a good salt substitute. Research should be done in order to discover something nontoxic and good tasting. Also, the FDA should require food processors to put an easily identifiable label on food stating whether it is high or low in salt. This sort of thing would at least help people to *reduce* their salt intake."

"I believe in the theory that atherosclerosis has its roots in the high cholesterol, high saturated fat diet," Dr. Freis said. "Low-saturated fat foods seem even more important than low cholesterol foods. It is argued that there is no proof for this theory—but there may never be proof because it's too difficult to carry out a controlled trial in a free-living society. How are you going to keep people in our society eating a low-fat, low-cholesterol diet for the 10 to 20 years which would be required for proof?"

How to screen for hypertension

The VA Cooperative Study clearly identified the value of antihypertensive therapy, but there are many thousands of hypertensives who remain unidentified. The solution to this problem, in Dr. Freis' opinion, is in carefully formulated community screening programs and in training all physicians to take the blood pressure of every patient they see. A pioneer in advocating large-scale screening, Dr. Freis has laid down some ground rules for a successful program.

- Prior arrangements must be made with physicians participating in the program, and the pace of the screening must be set by the numbers of patients these physicians can treat.
- Every patient with an initially high reading should be told to return very soon to have his pressure rechecked. Referral should only be done on the basis of the average of two or three readings.
- The screening personnel must be properly trained and their techniques should be checked before the program is begun.

Once the patient is referred, what are the criteria for treatment? Dr. Freis

developed an index of patient risk for individuals with various levels of hypertension. He assigns a score of

Dr. Freis: "When I began, I was trained to treat the crisis situation. Now, I work much harder at keeping people well...."

"1" to each of the following factors: male, black, age below 45 years, dia-

stolic pressure above 94 mm Hg on each visit, systolic pressure above 169 mm Hg on each visit, severe hypertensive complication in either parent, hyperlipidemia, or hyperglycemia. A risk factor of "2" is assigned to target organ damage. For the patient with an average diastolic pressure of 90-94 mm Hg, drug therapy is indicated if there is a risk score of "4." Drug therapy is begun if the patient has a risk score of "3" and blood pressure averaging 95-99 mm Hg diastolic, and for those patients with 100-104 mm Hg diastolic, a risk score of "2" mandates treatment. All patients with diastolic blood pressures averaging 105 mm Hg

or higher over three office visits should be treated no matter what their risk scores are.

Once the patient enters treatment, the program must be tailored to the individual, Dr. Freis emphasized. "In case of mild hypertension, changing a patient's life-style can be tried before drug therapy. Factors such as reduced salt intake, weight reduction, an exercise program, and elimination of smoking are all involved in reducing the risk of coronary disease and are valuable in their own right.

"If the patient's blood pressure is in the moderate range, I would begin drug therapy immediately, because

these are the patients at risk of developing hypertensive complications—"which are beautifully prevented by drugs. I don't want to take any risk of a patient getting a stroke or damaging his kidneys while using rather ineffective modalities of treatment."

Dr. Freis has found that thiazide diuretics will control about 50% of all hypertensive patients, while the remainder need, in addition, drugs which inhibit the activity of the sympathetic nervous system. He recommends the "stepped care" approach in which the physician carefully adds an adrenergically active drug to the initial diuretic, and finally a vasodilator to

the combination if blood pressure remains uncontrolled.

The greatest cause of treatment failure, Dr. Freis cautions, is non-

"We are coming to a time when we'll be able to control the degenerative diseases of old age."

compliance. "A patient who feels perfectly well is not likely to continue to take medication that makes him feel

sick." Dr. Freis' solution to the compliance problem: "tender loving care and education."

However, he recognizes few physicians have the time or interest to carry out the involved education program each hypertensive patient needs. This essential work, Dr. Freis stressed, should be carried out by nurses or trained paramedics. "The doctor should make the decision as to whether the patient should be treated and with what drugs, but the follow-up should be carried out by his assistants. We have a hypertension clinic at the Veterans Hospital with specially trained nurses, plus an educational program in

which the patients view films and listen to tapes. They are educated here, and the nurses give them that essential TLC. These patients seldom stop taking their medication because they are properly motivated."

The first effective antihypertensive agents were introduced in the early 1950s, and recently several new drugs have become available as antihypertensives. Among the newer drugs, Dr. Freis believes that the beta blockers—propranolol and metoprolol—have proven themselves. "A still newer agent which looks very promising, but has not yet been sufficiently investigated, is captopril," he commented. "This drug has a new type of action—it inhibits the enzyme which converts angiotensin I to angiotensin II." Angiotensin II is an active pressor hormone which causes vasoconstriction and hypertension when administered to normotensive patients.

As he looks back on his career, Dr. Freis realizes that his philosophy of medicine has changed. "When I began," he said, "I was a person who was trained to treat the crisis situation. Now, I work much harder at keeping people well, avoiding the crisis situation or delaying it as long as possible."

He believes that the medical profession as a whole is heading toward family practice and away from hyper-specialization. "It seems that the young doctors I see coming up take a much more positive attitude toward preventive medicine. Increasing numbers of them are disillusioned with the results of the treatment of crisis medicine, and they're not so fascinated with those fancy electronic toys as the first generation who received them."

Dr. Freis' own contribution to the practice of preventive medicine has not only saved countless Americans from crippling or fatal cardiovascular disease, but serves as a model for the kind of efforts needed to control other diseases. "We are now coming into a time when we'll be able to control the degenerative diseases of old age. Hypertension is the first cardiovascular disease of aging in which we have been able to show that treatment can to a large extent control the condition. Someday we may be able to do the same for atherosclerosis."

In Dr. Freis' Lasker Award Lecture in 1971, he concluded: "It has been my good fortune to have been engaged in antihypertensive drug research at a time when it was making great progress. Success in this field was achieved by empirical methods rather than by brilliant insights of solo investigators. The advances were made possible by the collaboration of many individuals both in industry and clinical pharmacology. These results justify the belief that with continued intensive efforts we can control all of the major cardiovascular diseases."

We can only speculate what the treatment of hypertension would be today without the contributions and inspired leadership of the VA Cooperative Study by Edward Freis. □